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**A rapid pathway toward a superb gene delivery system: programming structural and functional diversity into a supramolecular nanoparticle library.**

**Journal:** ACS Nano

**Publication Year:** 2010

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**PubMed link:** 20925389

**Funding Grants:** Microfluidic Platform for Screening Chemically Defined Conditions that Facilitate Clonal Expansion of Human Pluripotent Stem Cells

**Public Summary:**

Nanoparticles are regarded as promising transfection reagents for effective and safe delivery of nucleic acids into a specific type of cells or tissues providing an alternative manipulation/therapy strategy to viral gene delivery. However, the current process of searching novel delivery materials is limited due to conventional low-throughput and time-consuming multistep synthetic approaches. Additionally, conventional approaches are frequently accompanied with unpredictability and continual optimization refinements, impeding flexible generation of material diversity creating a major obstacle to achieving high transfection performance. Here we have demonstrated a rapid developmental pathway toward highly efficient gene delivery systems by leveraging the powers of a supramolecular synthetic approach and a custom-designed digital microreactor. Using the digital microreactor, broad structural/functional diversity can be programmed into a library of DNA-encapsulated supramolecular nanoparticles (DNA subsetSNPs) by systematically altering the mixing ratios of molecular building blocks and a DNA plasmid. In vitro transfection studies with DNA subsetSNPs library identified the DNA subsetSNPs with the highest gene transfection efficiency, which can be attributed to cooperative effects of structures and surface chemistry of DNA subsetSNPs. We envision such a rapid developmental pathway can be adopted for generating nanoparticle-based vectors for delivery of a variety of loads.

**Scientific Abstract:**

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